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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,322	CHU ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-12,14,15,17,18 and 20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-12,15,17,18 and 21-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants' election with traverse of Group I in the reply filed on February 28, 2007 is acknowledged. The traversal is on the ground(s) that the claims require a minimum of 10 sequences, and a meaningful election cannot be made of a single sequence. This argument is not persuasive because the requirement mailed May 16, 2006, was made based on the claims reciting "any gene from Table 3". The requirement is proper because each of the genes listed in Table 3 is patentably distinct. The search of the art for multiple genes would be burdensome on the Office and therefore an election of a single sequence is properly required. The requirement is still deemed proper and is therefore made ***FINAL***.

Status of Application, Amendments, and/or Claims

2. Claims 1-6, 8-12, 14, 15, 17, 18 and 20-33 are currently pending Claims 8, 14 and 20 are withdrawn as being directed to non-elected subject matter. Claims 1-6, 9-12, 15, 17, 18 and 21-33 are currently under examination with respect to the elected gene of Cyclin B.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 10-12 and 26-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Komarova et al. (Oncogene 1998).

With regard to claim 1, Komarova et al. teach a method of predicting whether a subject will be susceptible to undesirable toxicity resulting from treatment with an anti-proliferative therapy, said method comprising:

(a) obtaining an expression profile for at least 10 sequences selected from the 50 top ranked qenes set forth in Table 3 for a response to said anti-proliferative therapy in a sample from said subject (see p. 1095 col. 2 under *Materials and Methods* where expression profiles which included the gene Cyclin B were obtained from mice and cell cultures which were irradiated); and

(b) comparing said obtained expression profile to a reference expression profile to predict whether said subject is susceptible to undesirable toxicity (see p. 1089 col. 2 under results to p. 1090 col. 1, where the cell response to gamma irradiation in several types of cells were compared to their control counterparts. CDNAs from human or mouse were hybridized to human or mouse arrays and differential expression was analyzed. p53 responsiveness was a measure of toxicity).

With regard to claim 2, Komarova et al. teach the anti-proliferative therapy comprises administration of ionizing radiation (see p. 1095 col. 2 under *Gamma irradiation*, where gamma radiation was used).

With regard to claim 3, Komarova et al. teach the anti-proliferative therapy comprises administration of a chemotherapeutic agent that results in DNA damage (see p. 1095 col. 2 under *Gamma irradiation*, where gamma radiation, where gamma radiation meets the limitation of chemotherapeutic agent which results in a DNA damage).

With regard to claim 4, Komarova et al. teach the DNA damage comprises double-stranded breaks in DNA (see p. 1095 col. 2 under *Gamma irradiation*, where gamma radiation, where gamma radiation results in double stranded breaks in DNA).

With regard to claim 5, Komarova et al. teach a method of determining whether a subject is

susceptible to undesirable toxicity resulting from treatment with radiation therapy, said method comprising:

(a) obtaining an expression profile for the response to radiation for a sample for at least 10 sequences selected from the 50 top ranked genes set forth in Table 3 from said subject (see p. 1095 col. 2 under *Materials and Methods* where expression profiles which included the gene Cyclin B were obtained from mice and cell cultures which were irradiated); and

(b) comparing said obtained expression profile to a reference expression profile to determine whether said subject is susceptible to undesirable radiation toxicity (see p. 1089 col. 2 under results to p. 1090 col. 1, where the cell response to gamma irradiation in several types of cells were compared to their control counterparts. CDNAs from human or mouse were hybridized to human or mouse arrays and differential expression was analyzed. p53 responsiveness was a measure of toxicity).

With regard to claim 6, Komarova et al. teach the expression profile is a transcriptional profile (see p. 1089 col. 2 under results to p. 1090 col. 1, where, mRNA is used).

With regard to claim 10, Komarova et al. teach a method of determining whether a subject is susceptible to undesirable toxicity resulting from treatment with administration of a chemotherapeutic agent that induces double-stranded breaks in DNA, said method comprising:

(a) obtaining an expression profile for the response to said chemotherapeutic agent for a sample for at least 10 sequences selected from the 50 top ranked genes set forth in Table 3 from said subject (see p. 1095 col. 2 under *Materials and Methods* where expression profiles which included the gene Cyclin B were obtained from mice and cell cultures which were irradiated and irradiation meet the limitation of chemotherapeutic agent); and

(b) comparing said obtained expression profile to a reference expression profile to determine whether said subject is susceptible to undesirable toxicity (see p. 1089 col. 2 under results to p. 1090 col. 1, where the cell response to gamma irradiation in several types of cells were compared to their control

counterparts. CDNAs from human or mouse were hybridized to human or mouse arrays and differential expression was analyzed. p53 responsiveness was a measure of toxicity).

With regard to claim 11, Komarova et al. a method of predicting whether a subject will be susceptible to undesirable toxicity resulting from treatment with radiation therapy, said method comprising:

(a) obtaining an expression profile for the response to radiation for a sample for at least 10 sequences selected from the 50 top ranked genes set forth in Table 3 from said subject (see p. 1095 col. 2 under *Materials and Methods* where expression profiles which included the gene Cyclin B were obtained from mice and cell cultures which were irradiated); and

(b) comparing said obtained expression profile to a reference expression profile to determine the probability that said subject is susceptible to undesirable radiation toxicity (see p. 1089 col. 2 under results to p. 1090 col. 1, where the cell response to gamma irradiation in several types of cells were compared to their control counterparts. CDNAs from human or mouse were hybridized to human or mouse arrays and differential expression was analyzed. p53 responsiveness was a measure of toxicity).

With regard to claim 12, Komarova et al. teach the expression profile is a transcriptional profile (see p. 1089 col. 2 under results to p. 1090 col. 1, where, mRNA is used).

With regard to claim 26, Komarova et al. teach a method of obtaining an expression profile for the transcriptional response to radiation, the method comprising:

exposing a cell sample from an individual to radiation (see p. 1095 col. 2 under Gamma-irradiation);

extracting mRNA from said cell (see p. 1089 col. 2 under results to p. 1090 col. 1, where, mRNA is used);

quantitating the level of mRNA corresponding to at least 10 sequences selected from the 50 top ranked genes set forth in Table 3 (see p 1090 col. 1, where Komarova discloses the use of semi-quantitative RT-PCR).

comparing said level of mRNA to the level of said mRNA present in a cell sample from said individual not exposed to radiation (see p. 1089 col. 2 under results to p. 1090 col. 1, where the cell response to gamma irradiation in several types of cells were compared to their control counterparts. CDNAs from human or mouse were hybridized to human or mouse arrays and differential expression was analyzed using array hybridization, Northern blot analysis and RT-PCR).

With regard to claim 27, Komarova et al. teach the exposing to radiation comprises exposes said cell to a dose of ionizing radiation of from about 2 to about 10 Gy (see p. 1095 col. 2 under *Gamma-irradiation*).

With regard to claim 28, Komarova et al. teach the mRNA is extracted after at least about 2 and not more than about 24 hours following said exposure (see p. 1089 col. 2 under Identification of new p53 –responsive genes, where the mRNA was taken 4 hours after exposure to radiation).

With regard to claim 29, Komarova et al. teach further comprising exposing a cell sample from said individual to ultraviolet radiation at a dose of at least about 5 J/m2 and not more than about 50 J/m2 (Komarova is silent with respect to ultraviolet radiation, but ultraviolet radiation at this dose is a known equivalent to gamma radiation at the dose Komarova used).

With regard to claim 30, Komarova et al. teach the mRNA is extracted after at least about 4 and not more than about 72 hours following said exposure (see p. 1089 col. 2 under Identification of new p53 –responsive genes, where the mRNA was taken 4 hours after exposure to radiation).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Komarova et al. (Oncogene 1998) in view of Wahl et al. (USPN 6,251,362).

The teachings of Komarova et al. are presented above.

Komarova et al. do not teach the undesirable toxicity is grade 2.

Wahl et al. teach undesirable toxicity is grade 2 (see col. 10 lines 57-60).

One of ordinary at the time the invention was made would have been motivated to apply the method of gene expression analysis for radiation as taught by Komarova et al. with the specific toxicity grade of 2, as taught by Wahl et al. in order evaluate a genetic response to radiation toxicity with the accepted grading system. Wahl teaches that the grading system used to determine radiation toxicity is the NCI common criteria which encompasses grade 2 toxicity. Wahl evaluates radiation toxicity at grade 2 because it would be advantageous to avoid grade 2 toxicity in treatment protocols. It would have been prima facie obvious to apply the method of gene expression analysis for radiation as taught by Komarova et al. with the specific toxicity grade of 2, as taught by Wahl et al. in order to evaluate radiation toxicity using a standard grading system and to avoid toxicity at grade 2 in a treatment protocol.

5. Claims 17, 18 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. (USPN 6,015,673) in view of Komarova et al. (Oncogene 1998).

With regard to claim 17, Gonzalez et al. a method of determining the suitability of a patient for radiation therapy, the method comprising:

predicting whether a subject will be susceptible to undesirable toxicity resulting from treatment with radiation therapy, said method comprising:

(a) obtaining an expression profile for the response to radiation for a sample for at least 10 sequences selected from the 50 top ranked genes set forth in Table 3 from said subject (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil instead of radiation and DPD instead of Cyclin B); and

(b) comparing said obtained expression profile to a reference expression profile to determine the probability that said patient is susceptible to undesirable radiation toxicity (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil instead of radiation and DPD instead of Cyclin B); wherein a patient that is predicted to have a high probability of undesirable radiation toxicity is less suitable for radiation therapy (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil instead of radiation and DPD instead of Cyclin B).

With regard to claim 18, Gonzalez et al. teach the expression profile is a transcriptional profile (see col. 9 lines 55-57, where Gonzalez teaches mRNA).

With regard to claim 22, Gonzalez et al. teach a method of determining the suitability of a patient for treatment with an anti-proliferative chemotherapeutic agent that induces double-stranded breaks in DNA, the method comprising:

predicting whether a subject will be susceptible to undesirable toxicity resulting from treatment with said chemotherapeutic agent, said method comprising:

(a) obtaining an expression profile for the response to said chemotherapeutic agent for a sample for any gene from Table3 from said subject (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B); and

(b) comparing said obtained expression profile to a reference expression profile to determine the probability that said patient is susceptible to undesirable toxicity (see col. 2 lines 63-67 to col. 3 lines 1-6,

where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B);

wherein a patient that is predicted to have a high probability of undesirable toxicity is less suitable for said treatment with an anti-proliferative chemotherapeutic agent (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B).

With regard to claim 23, Gonzalez et al. teach a method of optimizing anti-proliferative therapy for a patient, the method comprising:

(a) obtaining an expression profile for the response to said anti-proliferative therapy for a sample for any gene from Table3 from said subject (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B); and

(b) comparing said obtained expression profile to a reference expression profile to determine the probability that said patient is susceptible to undesirable toxicity (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B);

wherein a dose of said anti-proliferative therapy is selected to minimize to undesirable toxicity, while providing for effective anti-proliferative activity (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B and see col. 7 line 34, where Gonzalez teaches adjusting the dose).

With regard to claim 24, Gonzalez et al. teach obtaining an expression profile for a response to one or more additional anti-proliferative therapies;

comparing said expression profiles to determine which therapy minimizes undesirable toxicity while providing for effective anti-proliferative activity (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B).

With regard to claim 25, Gonzalez et al. teach obtaining an expression profile for the response to said anti-proliferative therapy for (i) a normal cell sample for any gene from Table3 from said subject and (ii) a tumor cell sample for any gene from Table3 from said subject (see col. 2 lines 63-67 to col. 3 lines

1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B);

comparing said expression profiles from said normal cell and said tumor cell to determine which therapy minimizes undesirable toxicity while providing for effective anti-proliferative activity (see col. 2 lines 63-67 to col. 3 lines 1-6, where Gonzalez teaches 5'fluorouracil and DPD instead of Cyclin B).

With regard to claim 17, Gonzalez et al. do not teach radiation as the anti-proliferative therapy.

With regard to claims 17, 18 and 21-25, Gonzalez et al. do not teach Cyclin B.

Komarova et al. teach radiation exposure (see the abstract).

With regard to claims 17, 18 and 21-25, Komarova teach Cyclin B (see p. 1095 col. 2 under *Materials and Methods* where expression profiles which included the gene Cyclin B were obtained from mice and cell cultures which were irradiated).

One of ordinary at the time the invention was made would have been motivated to apply the method of gene expression analysis for chemotherapeutic toxicity as taught by Gonzalez et al. with the profile of Cyclin B as taught by Komarova et al. in order evaluate a genetic response to anti-proliferative agents. Komarova teaches that Cyclin B is a p53-response regulated gene and this gene is affected by radiation. Gonzalez teaches a method for evaluating a toxic response in an individual to the anti-proliferative agent of 5-fluorouracil using a gene expression profile. It would have been prima facie obvious to apply the method of using a gene expression profile to evaluate a genetic response to an anti-proliferative agent as taught by Gonzalez with the specific gene Cyclin B as taught by Komarova, in order to evaluate toxicity due to an anti-proliferative agent. There is a reasonable expectation of success because Cyclin B is necessarily effected by anti-proliferative agents as it is a p53 regulated gene.

6. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al. (USPN 6,015,673)and Komarova et al. (Oncogene 1998) in view of Wahl et al. (USPN 6,251,362).

The teachings and suggestions of Gonzalez et al. and Komarova et al. are presented above.

Gonzalez et al. and Komarova et al. do not teach or suggest the undesirable toxicity is grade 2.

Wahl et al. teach undesirable toxicity is grade 2 (see col. 10 lines 57-60).

One of ordinary at the time the invention was made would have been motivated to apply the method of gene expression analysis for radiation as taught by Gonzalez and Komarova with the specific toxicity grade of 2, as taught by Wahl et al. in order evaluate a genetic response to radiation toxicity with the accepted grading system. Wahl teaches that the grading system used to determine radiation toxicity is the NCI common criteria which encompasses grade 2 toxicity. Wahl evaluates radiation toxicity at grade 2 because it would be advantageous to avoid grade 2 toxicity in treatment protocols. It would have been prima facie obvious to apply the method of gene expression analysis for radiation as taught by Gonzalez and Komarova with the specific toxicity grade of 2, as taught by Wahl et al. in order to evaluate radiation toxicity using a standard grading system and to avoid toxicity at grade 2 in a treatment protocol.

7. Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Komarova et al. (Oncogene 1998) and Tibshirani et al. (PNAS, 2002).

The teachings of Komarova et al. are presented above.

Komarova et al. do not teach all of the limitations of claims 31-33.

With regard to claim 32, Komarova et al. teach a method of obtaining an expression profile for the transcriptional response in a phenotype of interest the method comprising

exposing a cell sample from an individual to said anti-proliferative therapy (see p. 1095 col. 2 under Gamma-irradiation)

extracting mRNA from the cell (see p. 1089 col. 2 under results to p. 1090 col. 1, where, mRNA is used)

quantitating the level of mRNA corresponding to a sequence of interest (see p 1090 col. 1, where Komarova discloses the use of semi-quantitative RT-PCR).

With regard to claim 33, Komarova et al. teach the phenotype of interest comprises anti-proliferative therapy (see, where radiation therapy meets the limitation of anti-proliferative therapy).

With regard to claims 31 and 32, Komarova et al do not teach the nearest shrunken centroid analysis of mRNA.

With regard to claims 31 and 32, Tibshirani et al. teach the nearest shrunken centroid analysis of mRNA (see the abstract).

One of ordinary at the time the invention was made would have been motivated to apply the method of gene expression analysis as taught by Komarova et al. with the analysis method as taught by Tibshirani et al. in order more accurately evaluate expression analysis data. Tibshirani states, "We have devided an approach to cancer class prediction from gene expression profiling based on an enhancement of the simple nearest prototype classifier. We shrink the prototypes and hence obtain a classifier that is often more accurate than competing methods (see abstract)." It would have been prima facie obvious to apply the method of of gene expression analysis as taught by Komarova et al. with the analysis method as taught by Tibshirani et al. in order to more accurately evaluate gene expression data with respect to cancer and tumors and treatment.

Summary

8. No claims were allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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05/23/2007